

Pharmacologic Advances in Orofacial Pain: From Molecules to Medicine

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Abstract: The management of chronic orofacial pain often follows a pattern of claims of efficacy based on clinical observations superseded by equivocal findings of effectiveness or belated recognition of toxicity. While therapeutic innovation spurred by genomics and proteomics is likely to result in new drugs for pain, inflammation, and neuropathic pain, the process of drug development and approval takes five to ten years and is often unsuccessful. Therapeutic strategies for improving treatment for chronic orofacial pain are proposed, but recognition of impediments to changing clinical practices suggest the need for interim measures. Greater understanding of the molecular and genetic events that contribute to pain chronicity and interindividual variations in pain responsiveness may eventually result in individualized molecular pain medicine to prevent and treat chronic orofacial pain.

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The management of chronic orofacial pain has a long history of therapeutic misadventures, charismatic-based treatment philosophies, controversies over nomenclature, and lack of scientific evidence for most clinical practices. The dental profession has struggled to develop a systematic approach to nomenclature, diagnosis, treatment, and clinical research through numerous conferences, workshops, and attempts at consensus. Despite these efforts, there is still no generally accepted professional agreement on the etiology and natural history of chronic orofacial pain, the role of occlusion, treatment needs, and the effectiveness, safety, and indications for most current practices.¹ Controversy over these questions is often fostered by a lack of appreciation for the difference between clinical observations, which may form the basis for therapeutic innovation, and the need to verify the safety and efficacy of treatments in studies that control for factors that can mimic clinical success. Tricyclic antidepressants, for example, arose from the clinical observations of astute clinicians but were subjected to scientific validation by well-controlled clinical trials.^{2,3}

A wide variety of drug classes have been described for temporomandibular disorders (TMD), ranging from short-term treatment with NSAIDs and muscle relaxants for pain of presumed muscular ori-

gin to chronic administration of antidepressants for less well-characterized pain. In general, claims of efficacy based on clinical observations are often superseded by equivocal findings of effectiveness or belated recognition of adverse effects and toxicity with long-term administration. The principles of pain management for TMD rest on the same principles that apply to the use of all drugs: demonstrated efficacy for the indication; an acceptable incidence of adverse reactions for the condition being treated; and safety when used in large numbers of patients for prolonged periods.

This article addresses the role of drugs in improving therapy for patients with chronic orofacial pain. Although emphasis is placed on the need for clinical research to validate currently used treatments, it is recognized that therapeutic innovation is more likely to occur through the development of novel agents for pain, inflammation, and neuropathic pain. Strategies are suggested to enhance this process as well as to minimize the transition from tissue injury and acute pain to pain chronicity by interfering with the development of plasticity in the nervous system. Greater understanding of the molecular and genetic events associated with chronic pain, combined with scientific validation of novel treatments, may lead to the ability to customize medicines for individual patients with greater efficacy and safety.

The Natural History of Therapies for Chronic Orofacial Pain

The natural history of therapeutic interventions for the management of chronic orofacial pain is illustrated in Figure 1.⁴ Novel treatments first described on the basis of initial case reports, case series, or poorly controlled clinical trials usually appear to have therapeutic benefit, or the results would not be published. Following evaluation of a putative therapy in well-controlled clinical trials, a number of alternative interpretations are possible. If several trials indicate that the treatment is effective and has minimum toxicity, it is then considered a validated therapeutic practice. An example of this outcome is the use of nonsteroidal anti-inflammatory drugs for the control of acute orofacial pain. If the treatment is found not to be effective, or if toxicity becomes evident, the drug is removed from the market, similar

to what occurred with zomepirac (Zomax) in the 1970s, or labeling restrictions are imposed, as was done for orally administered ketorolac (Toradol) more recently.

However, many therapies used for chronic orofacial pain do not fall under the jurisdiction of the Food and Drug Administration (FDA) as either drugs or devices and are not subjected to rigorous examination before being used in humans. Other review processes such as the U.S. Pharmacopeial Convention use expert panels to review non-FDA approved uses for marketed drugs but do not address devices or clinical practices. As a consequence, most drugs, devices, and therapeutic strategies used for chronic orofacial pain fall into the category of nonvalidated clinical practices. This does not imply that these treatment modalities do not have some therapeutic value. Rather, they have not been subjected to well-controlled trials that allow the biomedical community to determine whether the modality is a validated clinical practice whose efficacy exceeds the potential for toxicity or, possibly, that their use

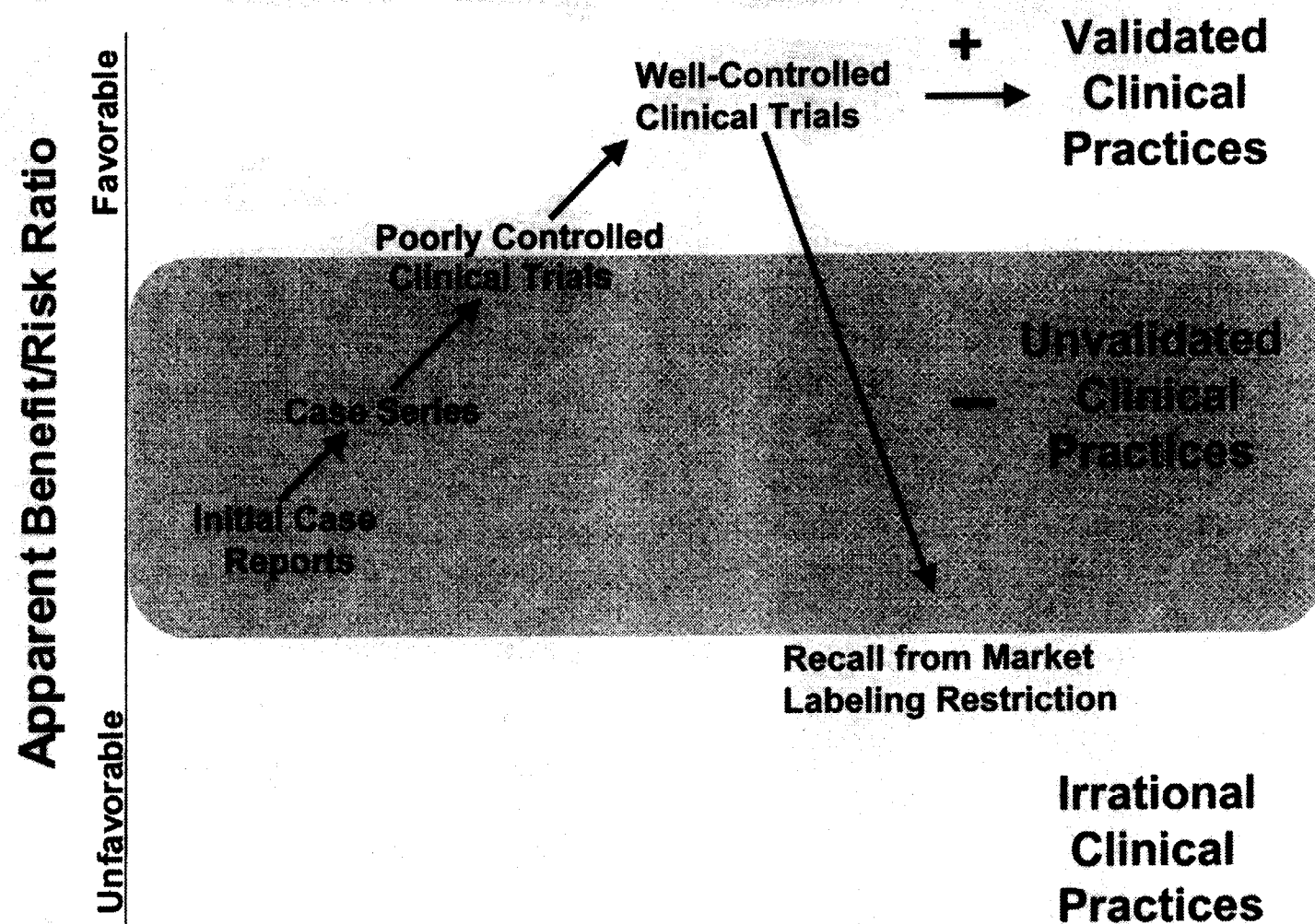


Figure 1. A schematic representation of the natural history of therapeutic modalities for chronic orofacial pain.

Initial favorable case reports and case series based on uncontrolled observations or poorly controlled clinical trials are superseded by well-controlled clinical trials, which are essential to evaluate a treatment's efficacy and safety. Publication of one or more well-controlled trials demonstrating a favorable benefit/risk ratio is considered adequate proof of a validated clinical practice. Failure to demonstrate efficacy or evidence of a lack of safety should result in removal from the market but may persist as an irrational clinical practice in an unregulated environment. Most treatments used for TMD have not been subjected to scientific validation and should be considered as unvalidated clinical practices.

represents an irrational clinical practice that should not be continued. The hazards of using a seemingly effective therapy in humans without appropriate validation of safety is illustrated by the use of Proplast implants for the treatment of TMD.^{5,6}

Another factor that may affect the evaluation of treatment outcome to drug therapy for TMD is the fluctuating nature of chronic pain, which may undergo remission and exacerbation independent of treatment.⁷ The high psychological comorbidity described in this population may also influence the onset of symptoms, reporting of pain intensity or its affective component, as well as treatment response. Many patients eventually improve, even if an initial course of therapy is not successful or if they receive no treatment at all. Such responses may explain the high rates of success reported in case series and loosely controlled studies for many of the therapeutic modalities used for TMD.

Improving Treatment for Chronic Orofacial Pain

The need to develop improved methods of pain relief for chronic orofacial pain (Table 1) is part of the larger problem of unmet needs for pain relief across the population for a variety of disease processes. Although the scientific basis for pain and analgesic mechanisms has been fostered during the past twenty-five years by scientific organizations (International Association for the Study of Pain, American Pain Society), increased funding support from the National Institutes of Health, and the explosion of knowledge in the neurosciences, progress in pain

Table 1. Steps to improved relief of chronic orofacial pain

Take advantage of scientific opportunities:

- Novel molecules and receptors as analgesic targets
- Genomically derived drugs
- Novel mechanisms based on proteomic insights

Enhance analgesic drug development:

- Improve clinical models and methodology
- Facilitate pharmaceutical research and development
- Participate in the regulatory process

Change clinical practices:

- Limit therapy to evidence-based practices
- Prevention and early treatment to minimize central plasticity
- Individualized molecular pain treatments

therapeutics has lagged. The scientific opportunities for greater understanding of pain and interindividual variation will likely parallel our increasing knowledge of novel molecular targets,⁸ the human genome,⁹ and its functional significance for gene expression under changing conditions.¹⁰ In the interim, a need exists to enhance analgesic drug development and therapy for pain indications not readily treated by currently available drugs such as NSAIDs or opioids and to change clinical practices to translate scientific advances into improved therapy.

Many impediments to improving pain relief (Table 2) delay or prevent the advancement of pain therapy at the same time that scientific knowledge is expanding. The pharmaceutical industry has long sought to develop drugs with increasingly specific mechanisms in hopes of minimizing the adverse ef-

Table 2. Impediments to improving therapy for chronic orofacial pain

Development of drugs with specific mechanisms of action for treatment of complex analgesic pathways and mechanisms

Limited clinical models for chronic pain to test the products of high throughput pharmaceutical research and development

- Current clinical models of pain validated with opioids and NSAIDs
- May miss activity of drugs acting through novel mechanisms

Extrapolating from homogeneous "clean" study samples to heterogeneous diseases and patient populations

- Most commonly used model for acute pain (oral surgery) detects drugs for acute inflammation, may not be relevant to molecular-genetic changes over time perpetuating chronic pain

Complex regulatory processes that discourage pharmaceutical research and therapeutic indications to areas not relevant to chronic orofacial pain

- Current regulatory guidelines for analgesic drug development based on expert opinions and consensus formulated in 1980s
- Rheumatoid and osteoarthritis indications may not be applicable to most forms of chronic orofacial pain

Lack of financial incentive for pharmaceutical interest in "orphan" diseases and populations

- Estimated \$500 million cost to develop new chemical entity not recoverable for small patient populations treated by a variety of nonpharmacologic and pharmacologic methods

Entrenched nonvalidated clinical practices

- Many clinical practices for treatment of chronic orofacial pain based on unproven etiologic hypotheses
- Most clinical practices have not been validated in appropriately designed clinical trials controlling for bias and regression of symptoms over time unrelated to the intervention

fects associated with virtually all clinically useful drugs. Pain mechanisms and pathways, however, are multifactorial, redundant, and closely linked to normal nociceptive transmission, an important protective physiologic process. Attempts to attenuate or block pain transmission with a single entity drug with a specific mechanism are often ineffective, as other facets of the pain process remain intact and can still signal nociceptive information. Recognition that plasticity occurs in the peripheral and central nervous system (CNS) in response to pain also complicates monotherapeutic strategies, as the initiating events being targeted may no longer be driving the processes sustaining pain perception. Conversely, therapy aimed at blocking or reversing the development of plasticity leading to pain chronicity holds promise as a novel therapeutic strategy based on our increased knowledge of pain physiology.

The development of selective cyclooxygenase-2 (COX-2) inhibitors is an example of improved pain therapy based on scientific observations, but also illustrates the time frame and level of pharmaceutical research and development needed to translate scientific opportunity into beneficial clinical practice. The introduction of traditional NSAIDs such as ibuprofen represented a significant improvement in efficacy and safety over previous treatments. Demonstration of analgesic efficacy in comparison to aspirin and opioid-containing combinations in a reliable model of acute pain¹¹ fostered the development of a number of NSAIDs for acute pain with resultant widespread use. Recognition that some drugs in the series produced unacceptable adverse effects led to the withdrawal of a number of the novel NSAIDs and closer evaluation of the toxic potential of the drug class. Basic research into the mechanisms of the arachidonic acid cascade led to the observation that cyclooxygenase (COX) exists as two isoforms, only one of which is normally present in most tissues.¹² It was hypothesized that the constitutive form, characterized as COX-1, was responsible for normal physiologic processes modulated by the production of prostaglandins and that the inducible form, COX-2, was responsible for the inflammatory sequelae of tissue injury and inflammation.¹³ This hypothesis, which has proven overly simplistic, fostered a research and development race among the major pharmaceutical firms to produce a drug with selectivity for COX-2 over COX-1. Such a profile would predict analgesic and anti-inflammatory efficacy with a reduced incidence of NSAID-toxicity.

The products of this pharmaceutical effort resulted in the introduction of celecoxib, in 1998, and rofecoxib, in 1999, for the treatment of arthritis and acute pain. The FDA required additional postmarketing studies to support claims of lower incidence of GI toxicity and renal effects. Although not unequivocal,^{14,15} the results of these studies are supportive of less gastrointestinal toxicity for selective COX-2 inhibitors in comparison to traditional dual-acting NSAIDs. A surprising finding was a higher rate in the rofecoxib group of nonfatal myocardial infarction, nonfatal stroke, and death from any vascular event.¹⁵ Cyclooxygenase-2 is constitutive in the kidney, being localized to the renal vasculature, the macula densa, and interstitial cells. Inhibition of homeostatic vasodilator responses account for most renal side effects associated with nonselective NSAID therapy. Postmarketing data for celecoxib shows an incidence of edema, hypertension, and exacerbation of pre-existing hypertension similar to the profile and incidence of nonselective NSAIDs.¹⁶ Although supportive of greater GI safety, additional information is needed on the pharmacology of coxibs to elucidate the cardiovascular and renal effects of these drugs and their potential interactions with low-dose aspirin, which is often taken prophylactically.¹⁷

The efficacy of the selective COX-2 inhibitors, however, is probably no greater than traditional NSAIDs (for review, see Dionne¹⁸) but at a substantially greater cost to patients, reflecting the approximately \$500 million cost associated with the preclinical and clinical development costs for a new drug. Thus, it took ten years from a molecular insight into the arachidonic acid cascade to result in an improved therapy for chronic pain with comparable efficacy and lower potential toxicity. No studies, however, have been published demonstrating a therapeutic advantage for the treatment of chronic orofacial pain with selective COX-2 inhibitors.

Changing Clinical Practices

The recognition that clinical dental practices should be based on reliable evidence has brought the dental profession into the realm of evaluating scientific evidence, usually in the form of controlled clinical trials. Unfortunately, the body of scientific data for the use of drugs to treat chronic orofacial pain is insufficient to apply formal assessment tools such as meta-analysis.¹⁹ As a consequence, clinicians have

continued to use treatments based on etiologic hypotheses (e.g., occlusal discrepancies, displaced articular disks, hyperactive muscles) that have never been subjected to rigorous scientific evaluation. Although many putative treatments are reversible and somewhat innocuous, surgical treatments are more likely to result in iatrogenic complications than therapeutic improvement, especially as the number of surgeries per patient increases.^{5,6} Drug treatments are also problematic, as the risk of adverse events usually increases with dose escalation or extended treatment, likely outcomes if initial treatment is not successful. NSAIDs, for example, have been associated with an increased incidence of gastrointestinal bleeding, renal dysfunction manifesting as end-stage renal disease requiring dialysis as the dose increases,²⁰ and increased mortality.²¹ Yet, little evidence exists that they have any therapeutic effects for the treatment of chronic orofacial pain,⁴ despite recommendations based on expert opinion.¹

The absence of a clear consensus among clinicians and researchers on the etiology and treatment of chronic orofacial pain fosters the continued use of surgical and orthopedic approaches for such unrelieved pain. The consequence of surgical interventions is illustrated by a case series of patients⁶ who had TMJ implants placed surgically that eventually failed and required additional surgery for implant removal and particle debridement. Many of these patients now report moderate to severe pain that has persisted for five to ten years, marked limitation of opening, and a severe negative impact on their quality of life. In the group reporting the highest level of pain, approximately 80 percent now have generalized muscular pain throughout their body satisfying the American College of Rheumatology criteria for fibromyalgia. Had this implant device been subjected to prospective evaluation for safety and efficacy, it is unlikely that the thousands of patients who received this device before clinical failures became apparent would have been similarly injured.

Other strategies for changing clinical practices for chronic orofacial pain (Table 3) include increased training of clinical researchers/orofacial pain specialists to provide doctoral training consistent with the principles of modern pain medicine, including the use and selection of therapeutic modalities. As described previously (see *The Natural History of Therapies for Chronic Orofacial Pain*), the availability and selection of therapeutic modalities for chronic orofacial pain are largely unregulated. Evidence for

the safety and efficacy of putative treatment modalities, whether currently used or investigational, is usually best derived from the results of controlled clinical trials. Treatments are randomly allocated among subjects to minimize investigator and patient biases and to ensure the validity of statistical tests that assume random allocation. Assessment of subjective symptoms such as pain requires blinded methodology to minimize the impact of preconceptions regarding which treatment is most efficacious and to control for placebo responses that can mimic therapeutic effects. An adequate sample size is needed to compensate for random variation among subjects and to provide assurance that apparent similarity between treatments does not occur by chance. Statistical tests are needed to quantify whether any difference among treatments is attributable to chance or represents a true therapeutic advantage. Unlike clinical practice, where patients who do not respond are discounted or lost to follow up, all subjects (both failures and successes) must be accounted for in the analysis of a controlled clinical trial. A role for clinical researchers/pain specialists in the doctoral education process would increase the likelihood that these principles would be taught adequately and be retained for critical evaluation by clinicians of putative, but untested, therapeutic modalities for chronic orofacial pain.

Table 3. Strategies for changing clinical practices for chronic orofacial pain

Limit therapy to evidence-based validated clinical practices

- Develop collaborative clinical trials to evaluate putative treatments in comparison to standard therapies and groups controlling for nonspecific improvements over time

Train more clinical investigators/pain specialists with scientific interest in mechanisms and treatment of chronic orofacial pain

- Foster enhanced academic standards for doctoral training
- Diagnosis and treatment of consistent with standards for pain medicine

Evaluate use of early interventions to minimize nociceptive input contributing to the development of central plasticity

- Treatments may be useful for interfering with molecular processes contributing to pain chronicity without classic analgesic profile

Evaluate individualized molecular pain medicine

- Match mechanism of interventions to the molecular-genetic profile of different chronic pain conditions
- Explore inter-individual genetic variations that may provide a basis for customizing medication selection and combinations to pain targets unique to the individual

Consensus among like-minded clinicians that a therapeutic modality in which they have expertise constitutes adequate evidence of efficacy and safety is no longer sufficient to reassure the public nor to protect from medico-legal liability when failures occur. The absence of any body that regulates clinical practices, combined with the inability to make scientific judgments because of an inadequate body of evidence, demonstrates the need to consider approaches to providing guidance to both patients and dental practitioners. Primary care practitioners not only initiate treatment at the earliest stages of symptom onset, but also direct patients to secondary care at the community level. Tertiary care for pain has become sophisticated with the development of pain management as a clinical specialty in medicine and as an unrecognized specialty in dentistry. Unfortunately, by the time a patient is referred to a tertiary care pain treatment facility, multiple treatments have failed, possibly with residual injury if a surgical modality was used, and pain chronicity may have developed. A tradition needs to be developed and fostered within the dental profession to identify and limit the clinical management of chronic orofacial pain to therapeutic modalities that have been scientifically demonstrated to be both safe and effective. In parallel, clinical research using generally accepted clinical trials methods needs to evaluate the safety and efficacy of commonly used treatments in a limited number of subjects and used as a criteria for evaluating any new therapeutic modality before it is widely used in large numbers of subjects.

Training More Clinical Investigators

The ability to conduct clinical evaluations of putative therapies for TMD and to capitalize on scientific opportunity will be limited by the number of well-trained clinical investigators with an interest in TMD therapy. Little is gained through case reports, case series, or poorly controlled clinical trials in comparison with the evidence gleaned from the results of well-controlled clinical trials. Although there is recognition of the need to base clinical practices on the results on data from controlled clinical trials, very few trials are actually published involving orofacial pain on an annual basis. This is a result, in part, of the dearth of clinical researchers across many disciplines, allegedly compounded by the inability of clinical

studies to get funded by NIH study sections. Recognition of this problem led to an NIH director's report in 1995 that documented the decreasing pool of academic clinical investigators. A subsequent report evaluated the funding success for clinical studies, supporting somewhat the problems of a clinical project receiving a competitive score in a traditional study section.

Several innovative programs have been initiated in an attempt to increase the number of trained clinical investigators addressing problems relevant to dentistry, such as orofacial pain.²² Career training awards specific for clinical investigators are now available for both training at extramural sites or in the NIH intramural research program. A loan repayment program helps clinicians with substantive educational debt repay up to \$35,000 a year while receiving clinical research training. The NIH Clinical Center has developed two clinical research-training programs in collaboration with major universities leading to an M.S. degree in clinical investigation. The NIDCR has developed a Clinical Research Training Fellowship, which offers up to three years of postdoctoral training in clinical research taking advantage of these NIH programs to produce a cadre of clinical investigators, some of whom specialize in orofacial pain. Training a new generation of clinical investigators who can progress rapidly from observation in a basic research laboratory to clinical investigation using molecular-genetic methods may herald a golden era in clinical research leading to novel insights into pain mechanisms and treatments.

Early Intervention to Prevent Central Plasticity

Given the futuristic orientation of the Distinguished Professor Program, consideration will be given to possible strategies for improved relief of orofacial pain based on recent observations in animal and clinical models. Animal studies of neurophysiologic mechanisms involved in pain processing demonstrate a prolonged excitation of sensory pathways following sustained nociceptive stimulation.^{23,24} This phenomenon, characterized as sensitization, has both peripheral and central components that result in a prolonged nociceptive input into the CNS long after the initial stimulus has ended. Animal studies also demonstrated that this process could be blocked by prior administration of a local anes-

thetic to the area of sensory stimulation and attenuated by prior administration of an opioid. A retrospective case series²⁵ supported a clinical application as preoperative administration of a local anesthetic or an opioid resulted in a delay in the onset of postoperative pain requiring analgesic administration. More controlled clinical investigations supported this hypothesis, which became described as preemptive analgesia.^{26,27} More critical examination of these observations and further clinical trials suggested that the local anesthetic had the same effectiveness for preventing postoperative pain if applied after the surgical event but prior to the onset of pain. Skeptics dismissed the concept of preemptive analgesia based on these later findings,²⁸ while others argued that this represented an equally important analgesic strategy that could be characterized as preventive analgesia.^{29,30}

Parallel studies in both animals and humans demonstrate that a receptor for excitatory amino acids in the CNS, the N-methyl-D-aspartate receptor (NMDA), plays a pivotal role in the development of sensitization there.³¹ The search for a clinically useful antagonist of the NMDA receptor led to a number of studies using the antitussive dextromethorphan because of its weak properties as an NMDA blocker. Most studies, using very high doses, demonstrated a decrease in both acute and chronic pain across a wide range of clinical conditions.^{32,33} The high doses required, however, resulted in an unacceptable incidence of side effects, making the approach untenable for most clinical indications. One pharmaceutical firm extensively evaluated combinations of a low dose of dextromethorphan with high doses of opioids to achieve an additive effect. The inability to reliably demonstrate a therapeutic advantage for a variety of doses and ratios of drug in comparison to administering the opioid alone, however, failed to result in FDA approval as a new therapy for chronic pain. The time course from initial scientific observations to failure to produce a new therapeutic strategy was approximately a decade and was conducted at great expense. New drugs with greater specificity at the NMDA receptor have demonstrated effects on the development of hyperalgesia, but with minimal effects on spontaneous pain³⁴ not predictive of clinical utility as a classic analgesic but possibly representing a novel analgesic strategy. Investigational compounds based on blocking the NMDA receptor may result in improved therapy for chronic pain, but the magnitude of this effect will likely be limited by the narrow specificity for only one of the many pathways initiating and sustaining chronic pain.

Opioids for Nonmalignant Pain

The long-term administration of opioids for nonmalignant pain is controversial. As recently as ten years ago, it was suggested that there is no place for opioids in the treatment of chronic benign pain.³⁵ Subsequent reports support the long-term administration of opioids for chronic nonmalignant pain. An open label study in one hundred patients with chronic pain for whom all other possible treatments had failed demonstrated good (51 percent) or partial (28 percent) pain relief with no signs of respiratory depression.³⁶ A more controlled trial evaluated sustained-release oral codeine in forty-six patients enrolled in a seven-day double-blind trial. Patients receiving the opioid reported significant analgesia and improvement on a pain disability index but with a higher incidence of nausea in comparison to placebo.³⁷ Another study evaluating the use of oral morphine (up to 60 mg twice daily) in a randomized, double-blind crossover study of six weeks duration in patients nonresponsive to codeine, NSAIDs, and antidepressants. The opioid produced significant pain relief with little effect on cognitive function or memory.³⁸ Although patients with head and neck pain were included in these studies, no data was reported on the use of long-term opioids for patients with TMD.

The long-term use of opioids in clinical practice was assessed in a survey of randomly selected physicians (N=1912).³⁹ The results of the survey indicate that prescriptions of opioids for long-term administration are widespread for the treatment of nonmalignant chronic pain in medical practice. Surprisingly, physicians in states that require multiple copies of prescription forms indicated a greater frequency of opioid prescriptions, which suggests that drug regulations are not a barrier to the use of opioids in clinical practice.

Most concern over the use of opioids centers on the potential for "addiction" and drug abuse. The term "addiction" implies the development of physical dependence and tolerance requiring continued opioid use with increasing doses. Physical dependence or the development of tolerance in a therapeutic context do not necessarily equate with addiction, as the maladaptive behavior associated with drug-seeking is not necessary if the drug is medically available. Similarly, cycles of intoxication and withdrawal

symptoms should not occur with sustained release formulations.

Recent reports in the lay press have called attention to the growing problem of abuse attributed to diversion of a controlled-release formulation of oxycodone (Oxycontin). Professional assurance that opioid abuse is minimal during the course of pain management is largely derived from data on cancer patients treated in tertiary care centers, clinical trials subject to selection biases, and limited survey data.⁴⁰ A study that is often cited reports a less than 1 percent risk of physical dependence among non-addicts in an acute care setting, not a chronic pain population with long-term opioid administration.⁴¹ At the other extreme, a case series suggests a high risk of aberrant drug-related behavior in patients receiving chronic opioids for nonmalignant pain.⁴² The problem attributed to Oxycontin is likely not related to the specific drug, but rather the basal rate of drug abuse in the United States and increasing availability of this medication because of its increased use for chronic pain.⁴³ With the incidence of drug abuse and experimentation in the U.S. population, any readily available opioid will be sought by this portion of the population, representing millions of substance abusers. The problem of drug abuse should not be attributed to Oxycontin or the use of opioids in pain management. Health care providers need to be aware of the potential for drug abuse among patients and diversion of drugs provided for therapy to illicit use. Strategies to minimize these problems include use of other pain medications in patients with a history of chemical dependence, dispensing small quantities, and requiring frequent re-evaluations in an appropriate pain management setting.⁴⁰

Developing Molecular Pain Medicine

The wide variation among patients in the response to tissue injury, the development of chronic pain after seemingly similar levels of trauma, and the response to analgesic drugs are suggestive of a genetic influence on pain. The use of inbred mice to produce genetically homogeneous strains has permitted testing of the genetic basis for pain using measures of nociception thought to be predictive of pain perception in humans. Mogil and colleagues have demonstrated a wide diversity in responsiveness to nociceptive stimuli across inbred strains and have

localized the genetic loci to areas containing genetic information for receptors known to play a role in pain processing, e.g., the opiate receptor.⁴⁴ Clinical investigations are now trying to determine whether these observations can be extended to humans and whether single nucleotide polymorphisms (SNPs) result in functional differences in pain perception.

A wide range of pain responsiveness has been demonstrated in two experimental models of acute pain: heat applied to the skin and immersion of a hand in an ice water bath.⁴⁵ Subtle differences in responses based on gender and ethnic background are suggestive of a genetic influence, but genotypic differences are not readily apparent, especially given the enormous number of genes (greater than 30,000) and SNPs (greater than 2 million) in the human genome. One variant of the delta opiate receptor has been demonstrated to result in a significant increase in sensitivity to heat in males but not females.⁴⁶ Although preliminary, this observation may be predictive of identifying genetic factors related to acute pain and can be tested for a relationship to the development of chronic orofacial pain.

Genetic factors also result in dramatic changes in gene expression in the spinal cord and brain over time in response to nociceptive stimuli.¹⁰ Neurons in pain pathways can actually change their phenotype from cells not encoding nociceptive information to responding in response to sustained tissue injury. The specific patterns of the phenotypic changes seen over time, the types of receptors expressed, and the response properties of neurons appear to differ over varying pain conditions. This phenomenon may represent a "molecular signal"¹⁰ that has to be considered in designing analgesic strategies for conditions as diverse as neuropathic pain, orofacial pain, or arthritis. The anatomical locus, the intensity, and the deleterious effects on quality of life may be similar, but a completely different mechanism may be operative requiring completely different treatment approaches.

Evolving from Molecules to New Medicines

A growing body of evidence supports the hypothesis that persistent pain may be the result, in part, of the development of central plasticity, not residual tissue, injury.^{23,24,31} This suggests that novel therapeutic approaches targeting molecules implicated in

the development or sustaining plasticity in the nervous system should be evaluated. Based on this hypothesis, pharmacologic treatments aimed at inhibiting central plasticity should be initiated at early stages of treatment rather than withheld until neural events may have become difficult to reverse.

Research strategies need to be considered to evaluate the hypothesis that molecular targets vary across different chronic pain conditions and over time within the same condition. In parallel, the genetic basis for interindividual differences in pain perception should be explored as another strategy for individualizing treatments for likely molecular targets. Identification of the “molecular signature” associated with differing pain syndromes and individuals may eventually permit development of rational analgesic combinations for multiple molecular targets. The unique nature of chronic orofacial pain suggests that greater interaction is needed between the dental research community, the pharmaceutical industry, and regulatory agencies to enhance analgesic development for a patient population too small to attract the huge investment needed to develop a new molecular entity into a clinical medicine.

Therapeutic Strategies for Orofacial Pain

As illustrated by the examples of the selective COX-2 inhibitors and the NMDA receptor blocker dextromethorphan, the time lag from scientific observation to new medication is approximately a decade, with a low rate of success. Although appropriate attention should be focused on the potential for new drugs from genomic and proteomic research, a need exists to validate currently used treatments to minimize risk to the patient. The limited data available from well-controlled clinical trials of the many categories of therapeutic interventions for chronic orofacial pain prevents use of systematic literature review techniques to evaluate most current therapies for chronic orofacial pain. Proponents of nonvalidated diagnostic methods and irreversible treatment modalities do not appear to appreciate the need to conduct such studies, making it unlikely that credible data will be forthcoming in the near future to support these clinical practices. Given the potential for iatrogenic injury associated with irreversible prosthetic and surgical interventions, educational and scientific efforts to promote improved care for

chronic orofacial pain should be limited to validated clinical practices. Until a therapeutic tradition and scientific literature develops based on evidence from controlled clinical trials, nonvalidated putative therapies should be considered as investigational, and patients should be fully informed of the risks inherent in the use of unproven modalities without certainty of a therapeutic effect.

Models exist for evaluating the efficacy and safety of therapeutic modalities in the absence of an FDA-approved drug, biologic, or device indication. The U.S. Pharmacopeial Convention has twenty-seven expert panels ranging from anesthesiology to urology, including dentistry, that evaluate off-label indications of drugs for inclusion in *USPDI Drug Information for the Health Care Professional* (Micromedex, Thompson Healthcare, Englewood, CO). A companion publication, *Advice for the Patient: Drug Information in Lay Language* (Micromedex, Thompson Healthcare, Englewood, CO) provides this information to the public with appropriate instructions for use, precautions, and side effects of each medication. The large number of diverse drugs and indications available for all medical conditions are evaluated by expert panels and published in separate volumes for professionals (>3200 pages) and for patients (>1600 pages). The much less complex and smaller volume of information relating to chronic orofacial pain treatments should be amenable to a similar approach and provide interim guidance as well as document areas in need of further research.

The Food and Drug Administration systematically evaluated the components of a wide variety of over-the-counter analgesics in the 1970s by use of expert panels to classify available drugs as generally recognized to be safe and effective, possibly effective but in need of further evaluation, or ineffective and subject to removal from the market. Drug combinations in need of further evaluation remained on the market for an extended period while manufacturers were permitted to reformulate these combinations or provide evidence that each component was safe and would contribute to the overall analgesic effectiveness of the combination. Newer drugs were then subjected to modern pharmacologic criteria for approval, eventually resulting in all marketed drugs having regulatory approval to assure the public of their safety. A similar approach could be used to characterize current treatments for TMD as generally recognized as safe and effective, possibly in need of further research, or nonvalidated.

The National Cancer Institute's Office of Cancer Complimentary and Alternative Medicine (NCCAM) has had a process since 1991 to evaluate data from alternative medicine practitioners of cancer patients treated with alternative medical approaches. The process, called the Best Case Series Program (<http://www.nci.nih.gov/occam/bestcase.html>), provides an independent review of the medical records, primary source materials, and pathology for an overall assessment of the evidence for a therapeutic effect. Data from best-case series are presented to an advisory panel for review and assessment; the panel uses these data to advise the NCCAM about promising complementary and alternative approaches for the treatment of cancer patients. If promising, the NCI supports rigorous scientific investigation of approaches with a positive review of best-case series by the advisory panel. Many of the issues that confound the assessment of complimentary and alternative medicine approaches apply to the use of surgical, dental, and mandibular orthopedic approaches to the treatment of chronic orofacial pain. It may be possible to adapt the best-case series approach with review and assessment by an appropriately constituted advisory panel to determine whether sufficient evidence warrants prospective, randomized trials. Proponents of surgical, dental, and mandibular orthopedic approaches, however, would have to be willing to come under scientific scrutiny to be eligible for research examining the legitimacy of their therapeutic methods.

These examples suggest that current putative therapies for chronic orofacial pain could be systematically reviewed by unbiased expert panels, possibly similar to the NIH Consensus Development Conference format, to arrive at interim evaluations of safety, efficacy, and the need for additional research to support therapeutic claims.

Development of a tradition of clinical trials and acceptance of criteria for evidence-based clinical practices would eventually permit better differentiation between treatments that have therapeutic value and others with potential for harm. Similarly, once individual treatments with demonstrated efficacy are identified, multiple therapeutic strategies could be evaluated in appropriately designed clinical trials. The growing appreciation that pain management is often palliative rather than curative could also be evaluated as a therapeutic goal to minimize patients' risk of iatrogenic injury with serially more aggressive treatments.

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